Wherein k represents a sample.

In the above equation, Θ represent the parameters of the IFS map.

Thus the output of step **110**, is a set of VDC coordinates, identified as VDC(k, Θ), with one set of coordinates for each enhanced dot spectrogram k = 1, 2...n.

The effect of the steps of **FIG. 3** is illustrated in **FIG. 4** which shows a set of dot spectrograms **450, 451 and 452** and a VDC **454**. As illustrated, each dot spectrogram is mapped to a point on the VDC.

COMMENTS

The above passage describes an alternate VDC construction method with equations that illustrate a canonical stochastic system which does not require an empirically constructed preliminary VDC (based upon known viral load studies). Therefore, a VDC can be constructed with as few as two viral load measurements. With regard to the mapping step, the above passages describes that as the mapping relates to a transformation of a microarray output, there is no need for data from a known viral load study to map the output patterns to the microarray and as few as two points may be used to map to the VDC.

Excerpt from Page 37, line 10 – Page 39, line 22:

Convergence Testing

Referring again to **FIG. 1**, once any uncertainty is compensated, the VDC coordinates are renormalized at step **114**. The renormalized VDC coordinates are patient specific and therapy specific. Alternately the coordinates could be virus / nucleotide marker specific. The NIF-compensated VDC coordinates are renormalized to the first diagnostic sample point obtained using the biomicroarray. Thus a patient can be referenced to any point on the VDC.

This renormalization step ensures that VDC properties are maintained, notwithstanding information uncertainties as indicated by the NIF correction terms. The approach is drawn from "renormalization-group" approach used for dealing with problems with many scales. In general the purpose of renormalization is to eliminate an energy scale, length scale or any other term that could produce an effective interaction with arbitrary coupling constants. The strategy is to tackle the problem in steps, one step for every length scale. In this

method the renormalization methodology is abstracted and applied during a posteriori regularization to incorporate information uncertainty and sample-to-sample variations.

This is in contradistinction to current viral load measurement calibration methods that either generate samples with same protocol and same assumptions of uncertainty or use some constant correction term. Both existing approaches skew the viral load readout so that measurements are actually accurate only in a limited "information" and "observability" context. This explains the large variations in readings from different laboratories and technicians for the same patient sample.

Specifically, we include the dynamic NIF correction function to the gradient of the VDC at the sample point normalized in a manner such that when the information uncertainty is null, the correction term vanishes. As discussed in the above steps, the NIF correction terms is actually derived from the noise statistics of the microarray sample.

$$< VDC'(k,\Theta) > = VDC(k,\Theta) \quad + \quad [\nabla NIF(Y,I)_k]$$

where $\nabla NIF(Y,I)_k$ denotes the gradient of nonlinear information prediction function. Under perfect observation model this term vanishes.

Once initialized, the VDC coordinates are then updated at step **116** applying the IFS filter W[ ] on k+1th sample, by

VDC(k+1, Θ)← W[Biomicroarray Output, K+1];

A direction convergence test is next performed at step **118** to determine whether the selected therapy has been effective. If convergence establishes that the viral load for the patient is moving in a direction representative of a lower viral load, then the therapy is deemed effective. The system is deemed to be converging toward a lower viral load if and only if:

$$\left\| \frac{VDC(t_k) - VDC(t_{k-j})}{VDC(t_{k-1}) - VDC(t_{k-j})} \right\| > 1 \quad \wedge \quad \left\| \frac{VDC_{peak} - VDC(t_k)}{VDC_{peak} - VDC(t_{k-1})} \right\| < 1 \quad \text{for } k > 2 \quad \text{and} \quad j > 0$$

The above relationships needs to be monotonically persistent for at least two combinations of k and j.

Also, date[k] - date[j] < κ * characteristic time, $\bar{t}$ (in days)

Where κ captures the population variability. Typically, $\kappa < 1.2$.

The peak VDC value is determined based on the VDC. The peak amplitude is an artifact of the specific parameterization to the Fokker-Planck

equation used in deriving the VDC. It is almost always derived independent of the specific sample.

In connection with step **118**, a VDC Shift factor Δ may be specified at which a dosage effectiveness decision and/or disease progression decision can be made. The VDC shift factor is applied to estimate the VDC curvature traversed between two measurements.

COMMENTS

The above passage discloses the usage of a VDC made without necessarily requiring any additional data from a calibrated viral load study. All the steps are computational geometry operators that exploit the VDC curvature geometry to make decisions on make viral load measurements and so only two points are necessary to generate the VDC.

Excerpt from Page 41, line 14 – Page 42, line 23:

Time Scale Testing

Next a determination has been made as to whether an effectiveness timescale has been exceeded at step **124** by:

Checking if a time step between successive sampling has exceeded T by determining if $Time_{k+1}$ - $Time_k$ > T

such that VDC(k+1, Θ)- VDC(k, Θ) < ς where

is set to 0.0001 and wherein

T is given by

$$T^* = \frac{1}{\omega} \arccos\left[1 - \frac{B(1/3,1/3)}{\sqrt[3]{2}} \frac{\alpha\sqrt{\omega}}{\gamma}\right]$$

B(1/3,1/3) represents the Beta function around the coordinates (1/3,1/3), We can actually use all B(1/2i+1,1/2i+1) for i>1 and i<7.

If $Time_{k+1}$ - $Time_k$ > T then output signal at step **126** indicating that either

no change in viral load concluded, OR
therapy deemed ineffective, OR
dosage deemed suboptimal.

If $Time_{k+1}$ - $Time_k$ < T then process another sample by repeating all steps beginning with Step 4 wherein a dot spectrogram is generated for a new sample.

If the effectiveness time scale has been exceeded then a signal is output indicating that no determination can be as to whether the therapy of interest is effective. If the time scale is not exceeded, then execution returns to step **106** for processing another sample. If available, and the processing steps are repeated.

COMMENTS

This passage again describes that the VDC usage dynamics do not require any reference to known viral load studies. The technique is based purely on computational geometry operators. The time scale matching imposes constraints on changes in viral load that step from change in patient condition as opposed to any artifacts of the quantitation process. In summary the entire process can be accomplished with as little as two points with or without reference to viral load.

CONCLUSION

Accordingly, for the above stated reasons, Applicant believes there is sufficient support for amended claim 8 and that the claims are not co-extensive with any of the claims in the '511 patent. If necessary, Applicant respectfully requests that the Examiner cancel newly submitted claims 26-33 if their continued prosecution would prevent the allowance of this application.

If the Examiner believes that a telephone call with Applicant (and the inventor, if needed) would expedite the prosecution of the current case, he is encouraged to contact the undersigned.

Respectfully submitted,

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I hereby certify that this correspondence is being faxed to the Assistant Commissioner for Patents, Washington, DC 20231 via 703.872.9307 by Carl Kukkonen on October 4, 2002.